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MEDICINAL CHEMISTRY RESEARCH

1,2,3,4-TETRAHYDROISOQUINOLINE ANALOGS OF PHENYLALKYLAMINE STIMULANTS AND HALLUCINOGENS

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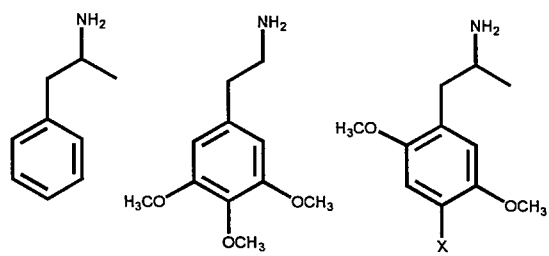
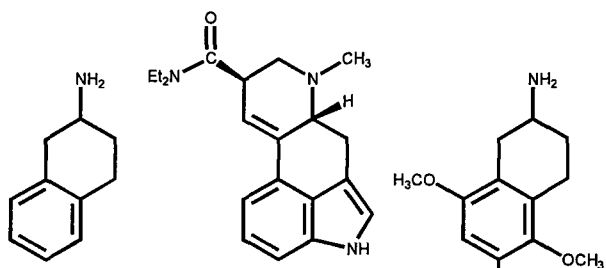
Abstract. Conformationally constrained, 1,2,3,4-tetrahydroisoquinoline (TIQ) analogs of central stimulant (e.g. amphetamine) and hallucinogenic (e.g. DOM) phenylalkylamines were prepared and evaluated to determine the contribution to activity of this conformational restriction. The amphetamine-related TIQs failed to produce locomotor stimulation in mice and did not produce amphetamine-appropriate responding in tests of stimulus generalization in (+)amphetamine-trained rats. Hallucinogen-related TIQs lacked appreciable affinity for 5-HT_{2A} serotonin receptors and did not produce DOM-like effects in tests of stimulus generalization in DOM-trained rats. It is concluded that the phenylalkylamine conformation represented by the TIQs is not a major contributor to these actions.

Depending upon the presence of various substituent groups, phenylalkylamines display central stimulant, hallucinogenic or other psychoactive properties [1]. For example, the stimulant amphetamine (**1**) is a simple aryl-unsubstituted phenylalkylamine whereas mescaline (**2**) is a prototypical phenylalkylamine hallucinogen. The influence of aromatic substitution on activity has been investigated, and it is known that an unsubstituted aromatic ring is optimal for amphetamine-like activity, and that hallucinogenic activity is typically associated with di- and tri-substituted aromatic rings [1]. Hallucinogenic potency is further dictated by the specific nature and location of these substituents [1]. For example, 1-(2,5-dimethoxy-4X-phenyl)-2-aminopropane, where X = CH_3 (DOM; **3a**) or Br (DOB; **3b**), are also hallucinogenic in humans with potencies of 80 and 400 times, respectively, that of mescaline (**2**) [2].



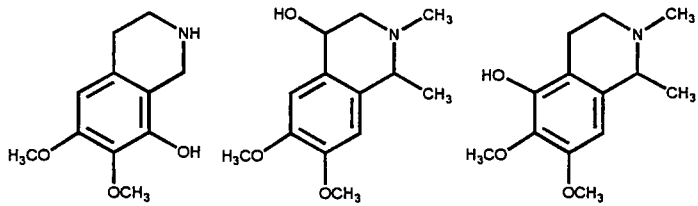
1 **2** **3**

Much less attention has been paid to the conformation of the phenylalkylamine side chain, and it is not known with certainty what conformation is optimal for stimulant or hallucinogenic activity, or whether the same or a similar conformation is optimal in both cases. With respect to amphetamine-like activity, there is some evidence that a fully extended side chain results in active agents. Constraining the side chain of amphetamine, as in 2-aminotetralin (2-AT; **4**), results in an agent that produces amphetamine-like stimulus effects in rodents. However, 2-AT (**4**) is only one-half [3] to one-eighth [4] as potent as amphetamine itself. Furthermore, 2-AT, unlike amphetamine, is inactive or only very weakly active as a locomotor stimulant in mice (e.g. see Oberlender and Nichols [4] for discussion). Thus, 2-AT may not represent an optimal, pharmacologically-relevant conformation for the stimulant actions of amphetamine. Alternatively, it may be homologation of the α-substituent of amphetamine that accounts for the reduced activity of 2-AT (**4**) [4]. Likewise, it is assumed that a fully extended side chain may be optimal for the hallucinogenic actions of the phenylalkylamines. This assumption is based, at least in part, on the observations that agents such as mescaline (**2**) produce effects similar to those of the hallucinogen lysergic acid diethylamide (LSD; **5**) [2,5], and that the phenylalkylamine component of LSD is present in the fully extended conformation. However, several studies have suggested that aminotetralin analogs of hallucinogens (e.g. **6a**, X = H; **6b**, X = -CH_3) may lack the actions of their more conformationally flexible counterparts [6-8]. Is it possible that some other conformation of the phenylalkylamines may better account for the actions of these agents?



4 **5** **6**

1,2,3,4-Tetrahydroisoquinolines (TIQs) represent another family of conformationally constrained phenylalkylamines. On the basis of unfavorable steric interactions it would seem unlikely that phenylalkylamines would readily adopt this conformation. Nevertheless, such a conformation might be induced upon interaction of a phenylalkylamine with a receptor. Is there any evidence to suggest that TIQs may be worth examining? Interestingly, the first alkaloid isolated from the hallucinogenic peyote cactus was a TIQ; in fact, of the first six alkaloids isolated only one (i.e., mescaline; **2**) was not a TIQ [9]. Approximately two dozen TIQs have been isolated from this plant and at least one, anhalamine (**7**) is classified as a hallucinogen [10]. Another TIQ, gigantine (originally assigned structure **8a**, but now believed to be **8b**) [11], has been shown to produce hallucinogenic reactions in squirrel monkeys and cats [12]. With respect to stimulants, Costall *et al* [13] have reported that N-methyl TIQ (i.e., **10**) produces hyperactivity in rats when injected directly into the nucleus accumbens. Thus, there have already been some reports to suggest that TIQs may possess hallucinogenic and stimulant properties.



7 8a 8b

In order to further explore TIQs, we prepared the amphetamine-related TIQs **9-12**, and TIQs related to the hallucinogens DOM (**3a**) and DOB (**3b**) (i.e., **14-18**). As a primary assay, the amphetamine-related TIQs were examined as locomotor stimulants, with (+)methamphetamine as positive control, whereas the hallucinogen-related TIQs were examined for their ability to bind at 5-HT_{2A} serotonin receptors. As a secondary assay, selected amphetamine-related TIQs were examined in tests of stimulus generalization in rats trained to discriminate (+)amphetamine from vehicle, whereas selected hallucinogen-related TIQs were examined in rats trained to discriminate DOM from vehicle.

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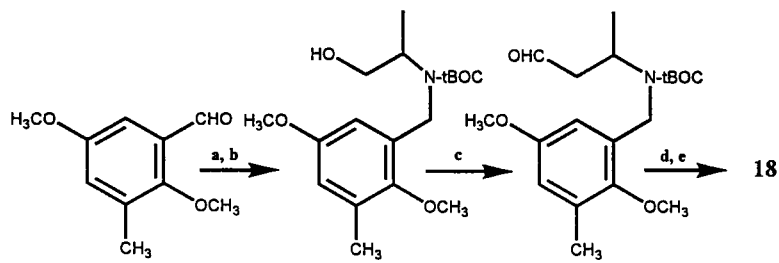
Some of the compounds used in this investigation have already been reported in the literature (see Experimental section); compounds **14-18** are new. Known 3-bromo-2,5-dimethoxybenzaldehyde was condensed with aminoacetaldehyde dimethylacetal to yield a product that was subsequently cyclized under acidic conditions to the hydroxyisoquinoline **15**; treatment of **15** with a diborane-pyridine complex afforded **14**. Compound **16** was prepared in an analogous manner from 2,5-dimethoxy-3-methylbenzaldehyde (**22**) except that the reduction step utilized catalytic hydrogenation. Treatment of **16** with formaldehyde and sodium cyanoborohydride gave **17**. With the same benzaldehyde as starting material, condensation with alaninol, followed by protection of the amine, afforded the corresponding hydroxyethyl derivative **23** (Scheme 1). The hydroxy group was oxidized to an aldehyde and cyclization was effected under acidic conditions to give the intermediate hydroxyisoquinoline; catalytic reduction provided **18**.



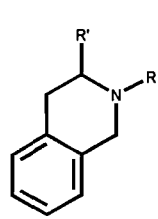
22 23 24

Scheme 1. **a.** Alaninol, H_2/Pd; **b.** $O(COOtBu)_2$; **c.** $(COCl)_2$, DMSO, CH_2Cl_2; **d.** 6*N* HCl; **e.** H_2/Pd.

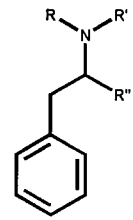
RESULTS

Stimulant-related TIQs. TIQs **9-12** were inactive as locomotor stimulants in mice relative to (+)methamphetamine (Table 1). That is, (+)methamphetamine (**13**) produced a dose-related increase in locomotor stimulation in mice, with 2 mg/kg producing a 625% increase over saline-treated controls. Under the same conditions, compounds **9** and **10** failed to produce a significant increase in locomotor activity. Compounds **11** and **12** produced saline-like effects even up to doses of 30 mg/kg. Likewise, phenylalkylamines **19 - 21** were also inactive at doses where (+)methamphetamine increased locomotor activity. Compounds **9**, **10**, and **11** failed to produce ≥ 80% (+)amphetamine-appropriate responding in rats trained to discriminate 1 mg/kg of (+)amphetamine from saline vehicle (Table 3). Compound **9** produced 46% amphetamine-appropriate responding at 5 mg/kg; however, at this dose, only 3 of 7 animals responded and response rates were severely depressed. Compounds **10** and **11** produced only saline-like effects (i.e., ≤ 20% amphetamine-appropriate responding) at doses of up to 9 mg/kg, which represents a dose of nearly 30 times the ED50 dose we have previously reported for (+)amphetamine (ED50 = 0.34 mg/kg) [14].

Table 1. Effect of amphetamine-related TIQs on the locomotor activity of mice.



A



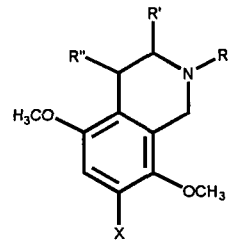
B

	Type	R	R'	R"	Locomotor Activity[a]
9	A	H	H	-	Inactive to 2 mg/kg
10	A	CH_3	H	-	Inactive to 2 mg/kg
11 (+)Isomer	A	H	CH_3	-	Inactive to 30 mg/kg
12 (+)Isomer	A	CH_3	CH_3	-	Inactive to 30 mg/kg
13 (+)Methamphetamine	B	H	CH_3	CH_3	Active at 0.5 - 2.0 mg/kg
19 (+)Isomer	B	CH_3	CH_3	CH_3	Inactive to 2 mg/kg
20	B	H	CH_3	H	Inactive to 2 mg/kg
21	B	CH_3	CH_3	H	Inactive to 2 mg/kg

[a] Compound **13** produced increases in locomotor activity as follows (dose, activity ±SEM): 0.5 mg/kg, 6928 (±1774); 1.0 mg/kg, 9212 (±948); 2.0 mg/kg, 23,168 (±1462) over water control (3704 ±380). All doses of **13** produced significant increases (Dunnett's t-test, $p < 0.001$), whereas the other agents failed to produce a statistically significant increase in locomotor activity relative to water control up to the dose indicated. Activity (±SEM) at the highest dose evaluated for each agent is as follows: **9**: 4111 (±597); **10**: 2909 (±454); **11**: 2545 (±207); **12**: 2124 (±541); **19**: 4422 (±423); **20**: 3566 (±279); **21**: 3762 (±525).

Hallucinogen-related TIQs. Compounds **14** (Ki = 242 nM; Table 2) and **16** (Ki = 2,150 nM) were found to bind with modest affinity at 5-HT_{2A} receptors, whereas **15**, **17**, and **18** were inactive (i.e., Ki > 10,000 nM). Compounds **14**, **16,** and **17** failed to result in stimulus generalization in DOM-trained rats (Table 3). Compounds **14**, **16**, and **17** produced a maximum of 2%, 5%, and 4% DOM-appropriate responding, respectively. Both DOM and DOB resulted in stimulus generalization; we have previously reported ED50 values of 0.44 and 0.20 mg/kg [15], respectively.

Table 2. Binding of hallucinogen-related TIQs at 5-HT_{2A} serotonin receptors.



	R	R'	R"	X	5-HT_{2A} Ki, nM (± SEM)[a]
14	H	H	H	Br	242 (20)
15	H	H	OH	Br	> 10,000
3b (DOB)					41[b]
16	H	H	H	CH_3	2,150 (250)
17	CH_3	H	H	CH_3	>10,000
18	H	CH_3	H	CH_3	> 10,000
3a (DOM)					100[b]

[a] [^{3}H]Ketanserin used as radioligand. With [^{3}H]DOB as radioligand, the following compounds displayed Ki values > 10,000 nM: **9**, **15**, **18**. Ki values for **14** and **16** = 250 (±80) and 2,650 (±50) nM, respectively. [b]Ki values were previously reported [16] and are included only for comparison.

DISCUSSION

Tetrahydroisoquinolines **9** and **10** failed to produce locomotor stimulation in mice and failed to result in stimulus generalization in amphetamine-trained rats. However, both lack the α-methyl group of amphetamine; moreover, compound **10**, although an analog of methamphetamine, is a tertiary amine, not a secondary amine. Compound **20,** the α-desmethyl analog of (+)methamphetamine (**13**), is inactive as a locomotor stimulant at doses where **13** displays a significant effect. Consequently, we investigated TIQs **11** and **12** which possess an α-methyl group; but these also proved to be inactive as locomotor stimulants even up to doses of 30 mg/kg. Compounds **10** and **12** are tertiary amines. Phenylalkylamine **19**, also a tertiary amine, is the N-methyl analog of (+)-methamphetamine (**13**); because **19** is less active than **13**, it is evident that tertiary amines are not as active as their secondary amine counterparts. This might explain why **10** and **12** are inactive as locomotor stimulants. It is difficult to draw any overall

Table 3. Results of stimulus generalization studies.

	Dose (mg/kg)	N[a]	% Drug-appropriate responding[b]	Resp/min[b]
(+)Amphetamine-trained animals				
9	2.0	5/5	8%	9.6
	3.0	7/7	36%	3.8
	4.0	7/9	39%	3.5
	5.0	3/7	46%	4.7
10	3.0	6/6	11%	13.0
	6.0	5/6	15%	8.8
	9.0	4/6	16%	5.7
11	1.0	7/7	8%	25.3
	3.0	7/7	4%	16.1
	6.0	6/6	20%	11.7
	9.0	6/6	17%	8.5
(+)AMPH[c]	1.0	7/7	92%	12.4
DOM-trained animals				
14	0.25	5/5	2%	16.2
	1.0	5/5	0%	13.8
	3.0	6/6	2%	11.5
	6.0	2/6	-[d]	
16	1.0	5/6	5%	8.6
	3.0	5/6	0%	11.9
	6.0	3/6	0%	5.2
17	1.0	6/6	4%	11.9
	3.0	5/6	2%	9.5
	5.0	2/6	-[e]	
DOB (**3a**)	0.4	4/5	91%	4.6
DOM[f] (**3b**)	1.0	6/6	96%	8.5

[a] Number of animals responding / number of animals receiving drug. [b] Data collected during a 2.5-min extinction session. [c] ED50 value (0.34 mg/kg) previously reported [14] [d] Disruption of behavior; majority of animals failed to make a total of 5 responses during the entire 2.5-min extinction session; the two rats that responded made 0% of their responses on the DOM-appropriate lever. [e] Disruption of behavior; the two animals that responded made 0% and 7% of their responses on the DOM-appropriate lever. [f] ED50 = 0.44 mg/kg [15].

conclusions from the present data because the lack of activity of **9** and **10** might be explained by the absence of an α-methyl substituent, and that of **10** and **12**, by virtue of their being tertiary amines. However, on the basis that (a) **11** meets both of these requirements (i.e., **11** is a secondary amine which possesses an α-methyl group) and yet fails to produce locomotor stimulation at 30 mg/kg, or stimulus generalization in (+)amphetamine-trained animals, and because (b) 2-AT (**4**) produces amphetamine-like stimulus effects in rats (albeit with a lower potency than amphetamine itself) [3,4], it must be concluded that the phenylalkylamine conformation represented by the TIQs is not as important as that represented by the aminotetralin conformation for producing these effects.

Phenylalkylamine hallucinogens bind at 5-HT_{2A} serotonin receptors, and there is a significant correlation between 5-HT_{2A} receptor affinity and both human hallucinogenic potency and drug discrimination-derived ED50 values for stimulus generalization where DOM is used as training drug [15,16]. Thus, hallucinogen-related TIQs were examined for their ability to bind at 5-HT_{2A} receptors (Table 2), and selected examples were further evaluated in tests of stimulus generalization in rats trained to discriminate DOM from vehicle (Table 3). The 5-HT_{2A} receptor affinities can be compared with some standard phenylalkylamine hallucinogens; for example, DOM (**3a**) (Ki = 100 nM) and DOB (**3b**) (Ki = 41 nM) have been previously shown to bind with high affinity at 5-HT_{2A} receptors [16]. The parent phenylalkylamine 2,5-DMA (**3**, X = H), which is also a hallucinogen [2], but one of low potency, binds with lower affinity (Ki = 5,200 nM) [16]. All three agents are recognized by DOM trained rats with ED50 values of 0.44, 0.20 and 5.51 mg/kg for DOM, DOB, and 2,5-DMA, respectively [15-17]. This provides us with a range of receptor affinities and ED50 values to serve as a guide. As expected, the parent TIQ **9** (Ki > 10,000 nM) does not bind at 5-HT_{2A} receptors. However, the TIQ analog of DOB binds with modest affinity (**14**; Ki = 242 nM, Table 2). On the basis of structural similarity to **8a**, the hydroxy analog of **14** (i.e., **15**) was prepared and evaluated, but **15** lacked affinity for 5-HT_{2A} receptors (**15**; Ki > 10,000 nM); apparently the hydroxyl group of **15** detracts from binding. The DOM analog of **14** (i.e., **16**) binds with reduced affinity (**16**; Ki = 2,150 nM), whereas the N-methyl and 3-methyl analogs of **16** are inactive (**17**, **18**; Ki > 10,000 nM).

On the basis of the binding data for **14** and **16**, it is expected that they might be recognized by animals trained to discriminate DOM from vehicle. However, both agents failed to produce DOM-like stimulus effects (both produced a maximum of ≅ 5% DOM-appropriate responding at approximately 10 times the ED50 dose of DOM; Table 3).

Ketanserin is a 5-HT_{2A} antagonist, and 5-HT_{2A} receptor binding studies are typically conducted with [^{3}H]ketanserin as radioligand. When a labeled agonist is used as radioligand, the affinity of 5-HT_{2A} agonists is enhanced whereas the affinity of 5-HT_{2A} antagonists is unchanged relative to their affinity for [^{3}H]ketanserin-labeled 5-HT_{2A} receptors [18]. For example the Ki values for DOM, DOB, and 2,5-DMA at agonist labeled (i.e., [^{3}H]DOB-labeled) 5-HT_{2A} receptors is 8, 0.79, and 268 nM, respectively [17]. The affinity (Ki) of **14** for agonist-labeled 5-HT_{2A} receptors is 250 nM, and that of **16** is 2,650 nM. The enhanced affinity expected of 5-HT_{2A} agonists was not seen, suggesting that **14** and **16** may not be agonists. This might explain why stimulus generalization did not occur with these agents in DOM-trained rats. Compound **14** was subsequently examined as a possible DOM-antagonist in tests of stimulus antagonism, however, a dose of 1.0 mg/kg given 30 min prior to the training dose of DOM

failed to produce any attenuation of effect (i.e., combination: 97% DOM-appropriate responding; 3.9 responses per min). Additional doses were not examined due to severely depressed response rates. A possible explanation for the lack of antagonism is that the affinity of this potential antagonist is significantly lower than that of antagonists which have been demonstrated to block the DOM stimulus, and higher doses of **14** might be required before an effect is seen. However, examination of such doses is precluded by the disruptive effects associated with high doses of **14**.

The present results suggest that the TIQ analogs of hallucinogenic phenylalkylamines may not reflect the conformations appropriate for binding at 5-HT_{2A} receptors, or for producing DOM-like stimulus effects in rodents. This prompted us to re-examine an aminotetralin analog of a phenylalkylamine hallucinogen. Compound **6a** (**6** where X = H) is the aminotetralin analog of 2,5-DMA. This compound binds at [^{3}H]ketanserin-labeled 5-HT_{2A} receptors with an affinity (Ki = 1,760 ±324 nM) [19] comparable to that of 2,5-DMA (Ki = 5,200 nM). Using an agonist radioligand (i.e., [^{3}H]DOB) to label 5-HT_{2A} receptors, the affinity of 2,5-DMA (Ki = 268 nM) [17] is enhanced by 20-fold. Compound **6b** binds at agonist-labeled sites with Ki = 74 (± 6) nM, also an enhancement of about 20-fold. Thus, in this one instance at least, the aminotetralin analog of a hallucinogenic phenylalkylamine behaves like the phenylalkylamine itself. Quantities of this compound were insufficient to allow for drug discrimination studies. These results, taken together with the above discussion of LSD, suggests that the aminotetralin conformation better represents the active conformation of the hallucinogenic phenylalkylamines than does the TIQ conformation.

In conclusion, there is no evidence to support the argument that the conformation represented by the TIQs is important for either the stimulant or hallucinogenic (i.e., DOM-like) actions of the phenylalkylamines. Although the specific substitution patterns found in anhalamine (7) and the TIQ **8** were not examined in the present study, it would be difficult to argue, on the basis of their being TIQs, that if indeed they are hallucinogenic, that they behave/act in a manner similar to the hallucinogenic phenylalkylamines. In contrast, the phenylalkylamine conformation represented by the aminotetralin structure, although perhaps (?) not optimal, better accounts for the amphetamine-like and DOM-like activities of the phenylalkylamines than does the TIQ conformation.

EXPERIMENTAL

Synthesis. Methylene chloride was dried by distillation over P_2O_5. Column chromatography was performed using silica gel (grade 62, 60-200 mesh, 150 Å). Melting points, determined on a Thomas-Hoover apparatus, are uncorrected. Proton magnetic resonance spectra were obtained with a GE QE-300 spectrometer, TMS was used as an internal standard. Elemental analyses were performed by Atlantic Microlab Inc. (Norcross, GA), and values are within 0.4% of theory. Commercially available free bases of **9** and **20** were converted to their known hydrochloride salts [20,21]. 3-Methyl TIQ **11** was prepared according to a literature procedure [22]; its 2-methyl derivative, although known [22], was synthesized using a general method for the preparation of tertiary amines using formaldehyde and sodium cyanoborohydride as described by Borch *et al* [23], and as exemplified for compound **17**. This same method was used for the N-methylation of **20** to **21**, which has been described in the literature by Sugama *et al* [24]. The 2-methyl TIQ **10** has been reported [25]; however, in the present study, it was prepared by N-methylation of **9** using the method described by Fitzgerald *et al* [26].

7-Bromo-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (14). A solution of **15** (0.8 g, 2.4 mmol) in H_2O (80 mL) was alkalinized by the addition of 5% NaOH to pH 12; extraction with CH_2Cl_2 (3 x 30 mL), drying of the combined organic portions (Na_2SO_4) and removal of the solvent under reduced pressure afforded the free base of **15** as a pale-yellow oil. Borane-pyridine complex [28] (1.0 mL, 8.0 mmol) was added in a dropwise manner to a stirred solution of this free base in CF_3COOH (20 mL) at 0 °C under a N_2 atmosphere. The reaction mixture was allowed to warm to room temperature and stirring was continued for an additional 12 h. The solvent was removed *in vacuo;* 10% NaOH (20 mL) was added to the residue and the resulting suspension was heated to 125 °C in an oil bath for 30 min then cooled to room temperature. The aqueous solution was extracted with toluene (3 x 30 mL), the combined organic portions were dried (Na_2SO_4), and the solvent removed under reduced pressure to give an oil which was purified by distillation [Kugelrohr, bp 175-185 °C (0.1 mmHg)]. The oil was dissolved in anhydrous Et_2O (40 mL) and treated with a saturated solution of HCl gas in anhydrous Et_2O to give a white solid hydrochloride salt. Recrystallization from absolute EtOH/ anhydrous Et_2O gave 0.3 g (43%) of **14** as a white crystals: mp 229-230 °C dec. ^{1}H NMR (DMSO-d_6) δ 2.75 (t, J = 6.3, 2H, CH_2), 3.30 (t, J = 6.3, 2H, CH_2), 3.71 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.21 (broad s, 2H, CH_2), 7.17 (s, 1H, ArH), 9.64 (broad s, 2H, NH^+_2). Anal ($C_{11}H_{14}BrNO_2$·HCl) C, H, N.

(±)7-**Bromo-5,8-dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (15).** 2-Hydroxy-5-methoxybenzaldehyde [27] (10.0 g, 64.4 mmol) was dissolved in glacial HOAc (50 mL); to this solution, cooled at 0 °C, was initially added freshly-fused CH_3COONa (6.0 g, 73.1 mmol), and then a solution of Br_2 (10.0 g, 62.6 mmol) in glacial HOAc (20 mL). The reaction mixture was allowed to warm to room temperature and stirring was continued for an additional 3 h; H_2O (30 mL) was added and the resulting solid was filtered and recrystallized from 90% EtOH to afford 12.3 g (83%) of 3-bromo-2-hydroxy-5-methoxy benzaldehyde as a yellow needles: mp 104-105 °C. 10% NaOH (10 mL) and a catalytic amount of benzyltriethylammonium chloride were added to a solution of this halo compound (0.2 g, 0.86 mmol) in CH_2Cl_2 (10 mL); the resulting emulsion was vigorously stirred for 12 h. The organic layer was separated and the aqueous portion was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic portions were dried (Na_2SO_4) and solvent removed at reduced pressure to give a semi-solid residue. This residue was purified by column chromatography using a solvent system of hexane/EtOAc (9:1) to give 0.2 g (94%) of 3-bromo-2,5-dimethoxybenzaldehyde as a white solid: mp 63-64 °C (lit [27] mp 64-65 °C).

A solution of above aldehyde (7.1 g, 28.7 mmol) and aminoacetaldehyde dimethylacetal (3.3 g, 31.3 mmol) in absolute EtOH (60 mL) was treated with PtO_2 (0.07 g) in a Parr hydrogenation bottle and hydrogenated at 15 psi overnight. The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated under reduced pressure to give an oil. The oil was purified by column chromatography using a solvent system of EtOAc/hexane (9:1) to give 6.0 g (62%) of 3-bromo-2,5-dimethoxy-N-(2,2-dimethoxyethyl)benzylamine as a pale yellow oil which was used without further characterization. A solution of the oil (6.0 g, 17.95 mmol) in 6*N* HCl (120 mL) was allowed to stir at room temperature for 3 days. The aqueous solution was concentrated at reduced pressure to a small volume (≈20 mL) to give a semi solid residue. Recrystallization from absolute EtOH and anhydrous Et_2O gave 1.2 g (21%) of **15** as a white crystals: mp 212-213 °C dec. ^{1}H NMR (DMSO-d_6) δ 3.16 (dd, J = 2.1, J = 12.6, 1H, CH_2), 3.66 (dd, J = 1.8, J = 12.6, 1H, CH_2), 3.71 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.17 (m, 2H, CH_2), 4.88 (broad s, 1H, CH), 5.71 (broad s, 1H, OH), 7.23 (s, 1H, ArH), 9.26 (broad s, 2H, NH^+_2). Anal ($C_{11}H_{14}BrNO_3$·HCl) C, H, N.

5,8-Dimethoxy-7-methyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (16). A solution of 2,5-dimethoxy-3-methylbenzaldehyde (22) [27] (3.2 g, 17.8 mmol) and aminoacetaldehyde dimethylacetal (2.1 g, 19.8 mmol) in absolute EtOH (60 mL) was hydrogenated (PtO_2: 0.01 g) and purified by column chromatography as described in the preparation of **15** to give 4.7 g (98%) of 2,5-dimethoxy-3-methyl-N-(2,2-dimethoxyethyl)benzylamine as a yellow oil. A solution of the oil (4.7 g, 17.4 mmol) in 6*N* HCl (110 mL) was stirred at room temperature for 24 h. The solution was transferred to a Parr hydrogenation bottle, treated with 10% Pd/C (1.6 g) and hydrogenated at 15 psi for 3 days. The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated under reduced pressure to a small volume (20 mL) to give the crystalline hydrochloride. Recrystallization from absolute EtOH/anhydrous Et_2O gave 2.7 g (65%) of **16** as white crystals mp: 223-224 °C. ^{1}H NMR (DMSO-d_6) δ 2.23 (s, 3H, CH_3), 2.76 (t, J = 5.9, 2H, CH_2), 3.29 (t, J = 5.9, 2H, CH_2), 3.62 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.15 (broad s, 2H, CH_2), 6.79 (s, 1H, ArH), 9.49 (broad s, 2H, NH^+_2). Anal ($C_{12}H_{17}NO_2$·HCl) C, H, N.

5,8-Dimethoxy-2,7-dimethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (17). A solution of **16** (0.8 g, 3.3 mmol) in H_2O (30 mL) was alkalinized by the addition of 5% NaOH to pH 12; extraction with Et_2O (3 x 40 mL), drying of the combined ethereal portions (Na_2SO_4) and removal of the solvent under reduced pressure afforded the free base as a pale yellow oil. To a stirred solution of the free base and 37% aqueous HCOH (1.5 mL, 18.7 mmol) in MeCN (15 mL) was added $NaBH_3CN$ (0.35 g, 5.3 mmol); a vigorous exothermic reaction ensued, and a residue separated. The reaction mixture was allowed to stir at room temperature for 15 min, and then glacial HOAc was added dropwise until the solution tested neutral on wet pH paper. Stirring was continued for an additional 45 min, glacial HOAc being added occasionally to maintain the pH near neutrality. The solvent was evaporated at reduced pressure and 2*N* KOH (20 mL) was added to the residue. The resulting mixture was extracted with Et_2O (3 x 30 mL); the combined ethereal extracts were washed with 0.5*N* KOH (1 x 20 mL) and brine (1 x 20 mL) then dried (Na_2SO_4) and solvent evaporated *in vacuo* to give an oil. The oil was dissolved in anhydrous Et_2O (40 mL) and treated with a saturated solution of HCl gas in anhydrous Et_2O to give a white hydrochloride salt. Recrystallization from absolute EtOH and anhydrous Et_2O gave 0.65 g (77%) of **17** as a white powder: mp 248 -249 °C. ^{1}H NMR (DMSO-d_6) δ 2.33 (s, 3H, CH_3), 2.95 (t, J = 5.6, 2H, CH_2), 3.02 (s, 3H, NCH_3), 3.27 (t, J = 5.6, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.38 (m, 2H, CH_2), 6.90 (s, 1H, ArH), 10.95 (broad s, 1H, NH^+). Anal. ($C_{13}H_{19}NO_2$·HCl) C, H, N.

(±)5,8-Dimethoxy-3,7-dimethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (18). A solution of 2,5-dimethoxy-3-methylbenzaldehyde (**22**) [27] (4 g, 22.2 mmol), DL-alaninol (1.86 g, 24.2 mmol) in absolute EtOH (60 mL) was treated with PtO_2 (0.08 g) in a Parr hydrogenation bottle and hydrogenated at 20 psi for 5 h. The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated under reduced pressure to give an oil which was purified by column chromatography using a solvent system of EtOAc/EtOH (9:1) to give 4.7 g (88%) of 2,5-dimethoxy-3-methyl-N-(1-hydroxy prop-2-yl)benzylamine as a pale yellow oil. Di-t-butyl dicarbonate (4.3 g, 19.6 mmol) was added to a solution of the above amine (4.7 g, 19.6 mmol) in EtOAc (100 mL) and the resulting mixture was allowed to stir at room temperature overnight. The organic layer was separated and the aqueous solution was extracted with EtOAc (3 x 50 mL); the combined organic fractions were washed with 5% HCl (2 x 50 mL) and brine (1 x 50 mL), dried (Na_2SO_4), and the solvent was removed *in vacuo* to give 6.6 g (99%) of 2,5-dimethoxy-3-methyl-N(1-hydroxyprop-2-yl)-N-(t-BOC)-benzylamine (**23**) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.11 (d, J = 6.6, 3H, CH_3), 1.43 (broad signal, 9H, $C(CH_3)_3$), 2.26 (s, 3H, CH_3), 3.57 (d, J = 7.9, 2H, CH_2), 3.67 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.05 (m, 1H, CH), 4.47 (broad s, 2H, CH_2), 6.63 (d, J = 2.0, 1H, ArH), 6.70 (d, J = 2.0, 1H, ArH).

A solution of dry DMSO (4.6 mL, 62 mmol) in dry CH_2Cl_2 (6 mL) was added in a dropwise manner to a stirred solution of oxalyl chloride (2.8 mL, 32.0 mmol) in dry CH_2Cl_2 (60 mL), cooled to -60 °C, under an N_2 atmosphere. When the addition was complete, the reaction mixture was allowed to stir for 2 min, then a solution of protected amine **23** (6.4 g, 18.8 mmol) in dry CH_2Cl_2 (25 mL) was added in a dropwise manner; stirring was continued for an additional 30 min. NEt_3 (19 mL, 135.6 mmol) was added and the reaction mixture was allowed to warm to room temperature; H_2O (70 mL) was added and the aqueous layer was reextracted with additional CH_2Cl_2 (3 x 40 mL). The organic layers were combined, washed with 1% HCl (2 x 40 mL), 5% Na_2CO_3 (2 x 40 mL), and brine (1 x 40 mL), then dried (Na_2SO_4); solvent was removed *in vacuo* to give 6.3 g (99%) of **24** as a yellow oil. A solution of the aldehyde (5.0 g, 14.8 mmol) in 6*N* HCl (150 mL) was allowed to stir at room temperature for 24 h. The solution, in a Parr hydrogenation bottle, was treated with 10% Pd/C (1.5 g) and hydrogenated at 15 psi for 5 days. Catalyst was removed by filtration through a Celite pad and the filtrate was concentrated under reduced pressure to give a solid. Recrystallization from 2-PrOH gave 0.9 g (22%) of **18** as a white solid: mp 246 247 °C. ^{1}H NMR (DMSO-d_6) δ 1.61 (d, J = 6.5, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.65 (dd, J = 10.5, J = 18.0, 1H, CH_2), 3.14 (dd, J = 4.4, J = 18.0, 1H, CH_2), 3.65 (m, 1H, CH), 3.84 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.40 (broad signal, 2H, CH_2), 6.95 (s, 1H, ArH), 9.5-10.0 (broad signal, 2H, NH^+_2). Anal. ($C_{13}H_{19}NO_2$·HCl) C, H, N.

Pharmacology

Radioligand binding studies. For the radioligand binding studies, human cells were grown and harvested, and competition assays were performed, as previously reported [29] using either [^{3}H]ketanserin or [^{3}H]DOB [18] as radioligands.

Drug discrimination studies. Groups of male Sprague-Dawley rats were trained to discriminate either 1.0 mg/kg of (+)amphetamine sulfate or 1.0 mg/kg of (±)1-(2,5-dimethoxy-4-methylphenyl)-2-amino propane hydrochloride (DOM) from 0.9% saline vehicle, administered via intraperitoneal injection 15 min before testing, under a variable interval 15 s schedule of reinforcement for sweetened milk reward using standard 2-lever operant chambers. We have previously described this method in detail [14]. The amphetamine-trained animals are those that we recently trained to examine clobenzorex [30], and the DOM-trained animals are those we recently trained to examine a metabolite of risperidone [31]. Where stimulus generalization (i.e., > 80% drug-appropriate responding) occurred, ED50 values were calculated by the method of Finney [32].

Locomotor activity studies. Albino ICR mice (male and female) weighing 25-30 g were used throughout the study. Male and female mice were housed separately in groups of five on a 12-h L : 12-h D cycle at a room temperature of 21 ± 1 °C with free access to food and water. All experiments were performed between 0800 and 1700 h. On the test day, animals were acclimated in black plastic dummy observation cages (28 x 28 x 28 cm) for 30 min prior to drug administration. The animals were then administered water vehicle or drug via intraperitoneal injection. Compounds were examined at multiple doses; compounds **9**, **10**, **13**, **19**, **20**, and **21** were examined at 0.5, 1.0, and 2.0 mg/kg, and compounds **11** and **12** were examined at doses of 1, 3, 10, and 30 mg/kg. All doses of all compounds were examined in 5 to 7 animals. Following injection, animals were returned to the dummy observation cages. Ten minutes later, the mice were transferred and placed individually in four black experimental observation cages of similar dimension. Locomotor activity, measured as distance traversed (in cm), was recorded for the next 40 min by a computerized video tracking and behavior recognition system [Ethovision (version 1.7), Noldus Information Technology, Costerweg, Netherlands].

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